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Perspective

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The Next Phase of Human Gene-Therapy Oversight

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The National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have played key roles in the emergence of safe and effective human gene therapies. Now, we are proposing new efforts to encourage further advances in this rapidly evolving field.

The potential to alter human genes directly was first recognized nearly 50 years ago, around the same time as initial groundbreaking advances were being made in recombinant DNA technology. After intense discussions regarding the ethical, legal, and social implications of this technology, conversations were initiated at the NIH that led to the establishment of the Recombinant DNA Advisory Committee (RAC) in 1974. The RAC's mission was to advise the NIH director on research that used emerging technologies involving manipulation of nucleic acids — a mission that was eventually expanded to encompass the review and discussion of protocols for gene therapy in humans. In 1990, the FDA oversaw the first U.S. human gene-therapy trial, which involved pediatric patients with adenosine deaminase deficiency and was conducted at the NIH Clinical Center in Bethesda, Maryland.

Although no major safety concerns were initially reported, over the course of the 1990s it became evident that many questions regarding the safety and efficacy of gene therapy remained unanswered. These unknowns were brought into sharp focus in 1999 when Jesse Gelsinger died of a massive immune response during a safety trial of gene therapy for ornithine transcarbamylase deficiency.[1] This tragic death led to closer scrutiny of the field, including a greater focus on open dialogue and increased regulatory oversight.

Since that time, a tremendous amount of scientific work related to gene therapy has been conducted with support from government agencies, academic institutions, and commercial sponsors. These efforts have increased understanding of the basic biology of the diseases being treated, the various methods used for gene delivery, and the potential adverse events that can be encountered. Progress has also been made in improving safety precautions, as well as gene-transfer efficiency and delivery.

As science advanced, along with the ability to apply these innovations, gene therapy has evolved from offering modest effects in early trials to producing measurable benefits in the clinic. In 2017, the FDA approved the first three gene-therapy products for use in the United States. Two are cell-based gene therapies — chimeric antigen receptor T-cells (CAR-T) — that have demonstrated remarkable efficacy against cancer in clinical trials.[2] The third, which treats retinal dystrophy caused by *RPE65* gene mutations, is the first approved gene-therapy product to be administered in vivo and the first to target a specific genetic condition. Given the field's rapid evolution, and the fact that the FDA currently has more than 700 active investigational new drug applications for gene therapies, it seems reasonable to envision a day when gene therapy will

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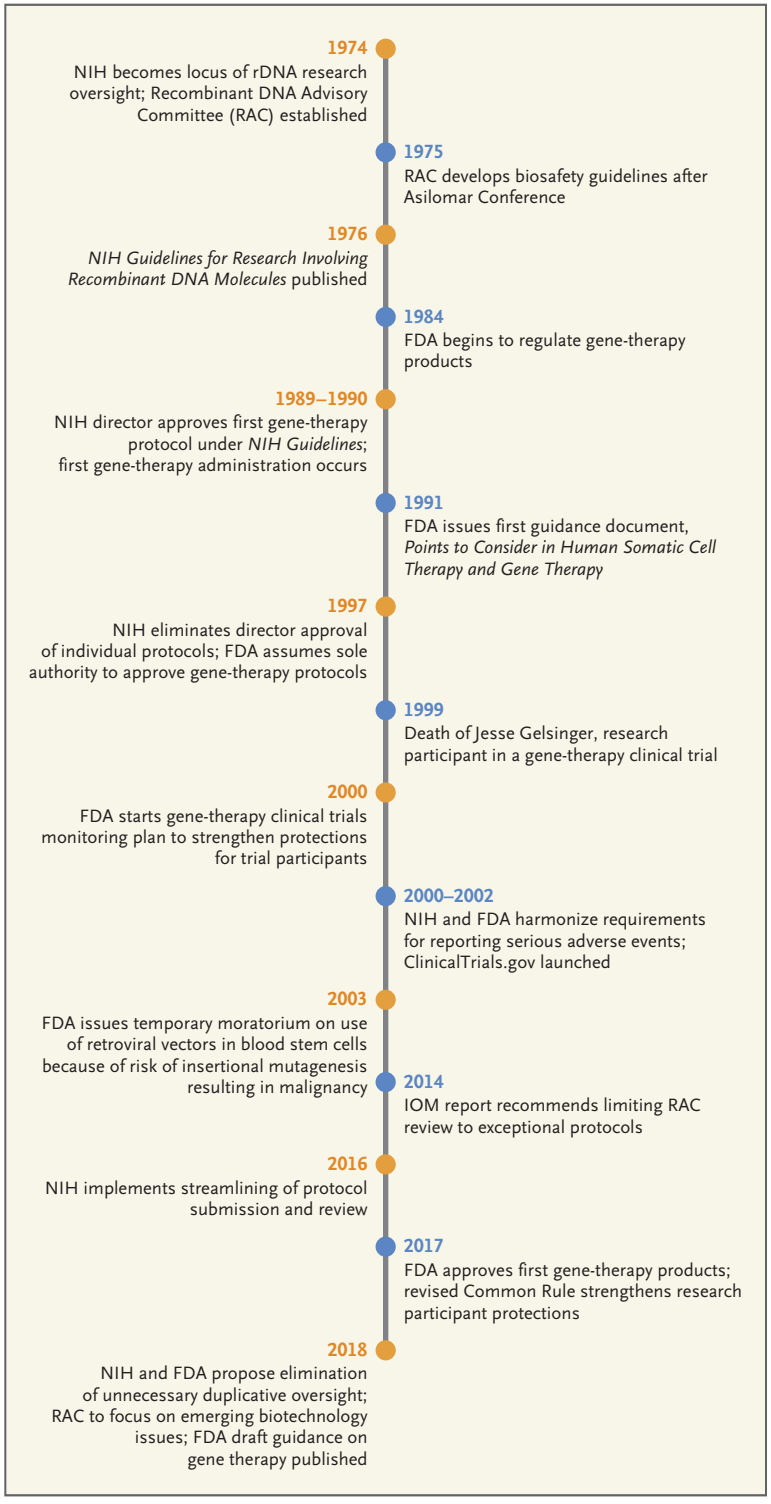

History of Gene Therapy NIH–FDA Oversight.

IOM denotes Institute of Medicine, and rDNA recombinant DNA.

be a mainstay of treatment for many diseases.

Though still more needs to be learned about the safety and efficacy of current technologies, many promising new approaches are on the horizon. For example, the advent of genome editing opens new possibilities for treating diseases that might be challenging or impossible to address with gene-transfer technologies. The capacity for editing genes using zinc finger nucleases (ZFNs), transcription activator–like effector nucleases (TALENs), and meganucleases has existed for decades. But the field made a quantum leap forward about 5 years ago with the discovery and development of the CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 gene-editing system.[3] Already, researchers have announced the first in vivo clinical trial of genome editing to correct Hunter's syndrome by means of ZFNs, and CRISPR-Cas9 and TALENs gene-editing approaches are being explored in the clinic for T-cell immunotherapy. Clinical trials for sickle cell disease are expected soon.

As gene therapy continues to change, so must the federal framework set up to oversee it. Over the years, this system has been modified in response to our growing understanding of scientific advances and their associated risks (see timeline). For example, after Gelsinger's death, the NIH and the FDA collaborated on the development of the Genetic Modification Clinical Research Information System (GeMCRIS), a database designed to assist in tracking gene-therapy products, monitor trends in the field, and provide transparency through a public-facing website. In addition, human-subjects research protections will be improved through changes that updated provisions of the Common Rule. In July 2018, the FDA released a suite of draft guidance documents pertaining to gene therapy that proposes new guidance on manufacturing issues,

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long-term follow-up, and pathways for clinical development in certain areas, including hemophilia, ophthalmologic indications, and rare diseases.[4]

Still, more changes are needed to safely expedite progress, and now is an opportune time to reevaluate the U.S. oversight system for gene-therapy trials. As the NIH, the FDA, and research entities have moved to strengthen their individual oversight efforts, some overlaps have occurred. For example, substantial duplication has arisen in the submission of initial protocols, annual reports, amendments, and reports of serious adverse events. Originally, these overlaps — which affect no other field of biomedical research — were viewed as harmonized reporting that enabled the FDA to conduct regulatory oversight while maintaining confidentiality with sponsors and allowed the NIH to provide transparency with regard to the research. But the intervening implementation of ClinicalTrials.gov has resulted in a high level of transparency for many gene-therapy trials conducted by both public and private sponsors.

In the view of the senior leaders of the FDA and the NIH, there is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable — or that the field still requires special oversight that falls outside our existing framework for ensuring safety. Although scientific and safety challenges do remain — improving gene-transfer and gene-editing efficiencies, addressing immune responses and cytokine release syndrome, and in the case of gene editing, delivery and off-target effects — the robust clinical research oversight system already accommodates for the fact that each field of research has associated unique challenges. Even as our understanding of gene therapy has advanced, so has our general framework for medical product safety. The tools we use to address other areas of science are now well suited to gene therapy.

The NIH has, in fact, already started down the path toward integrating gene therapy within the existing oversight system, by making changes to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* and modifying the RAC's role. In 2013, the NIH requested that the Institute of Medicine assess the RAC's review of gene-therapy protocols,[5] and in 2016, the NIH implemented recommendations from the report by limiting RAC review to human gene-therapy protocols that raised exceptional issues or concerns. Since that change took effect, the NIH has determined that only 3 of 275 such protocols warranted RAC review.

In changes proposed on August 17, 2018, in the *Federal Register*, the NIH and the FDA seek to reduce the duplicative oversight burden by further limiting the role of the NIH and RAC in assessing gene-therapy protocols and reviewing their safety information. Specifically, these proposals will eliminate RAC review and reporting requirements to the NIH for human gene-therapy protocols. They will also revise the responsibilities of institutional Biosafety Committees, which have local oversight for this research, making their review of human gene-therapy protocols consistent with review of other research subject to the *NIH Guidelines*. Such streamlining will also appropriately place the focus of the *NIH Guidelines* squarely back on laboratory biosafety.

We thus have an opportunity to return the RAC to the spirit in which it was founded. Its original goal was to advise the NIH director on the scientific, safety, and ethical issues associated with emerging biotechnology. With the continued emergence of new biotechnologies beyond the realm of recombinant DNA, the RAC's role must evolve.

The NIH envisions using the RAC as an advisory board on today's emerging biotechnologies, such as gene editing, synthetic biology, and neurotechnology, while harnessing the attributes that have long ensured its transparency. We at the NIH and the FDA look forward to working together with all our stakeholders to implement these changes. We share common goals: advancing science and human health and accelerating the availability of safe and effective gene therapy, along with the many promising new products that future biotechnologies may bring.

Disclosure forms provided by the authors are available at NEJM.org.

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